

# Diabetes Medications in CKD

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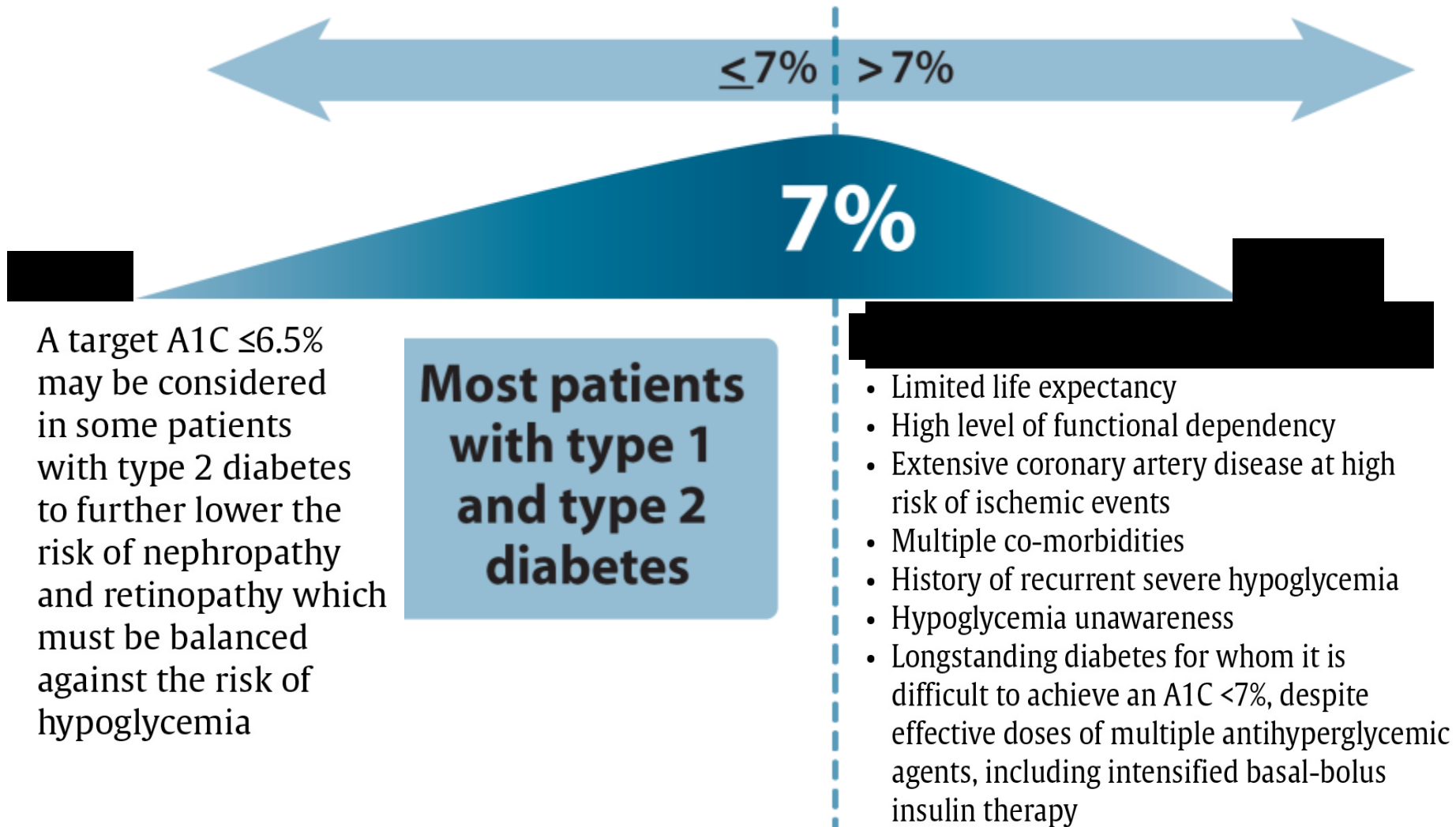
# Objectives

- Broadly review the current agents used for glycemic management in Type 2 DM
- Understand the indications and contraindications for selected medications used in Type 2 DM in the setting of the stages CKD
- Consider the evidence supporting the recommended medication adjustments in CKD

# CDA 2013 Guidelines: Glycemic Management in T2DM

- ✓ **CHOOSE** initial therapy based on **glycemia**
- ✓ **START** with **Metformin** +/- others
- ✓ **INDIVIDUALIZE** your therapy choice based on characteristics of the **patient** and the **agent**
- ✓ **REACH TARGET** within **3-6 months** of diagnosis

# Individualizing A1C Targets



**AT DIAGNOSIS OF TYPE 2 DIABETES**

A1C <8.5%	A1C ≥8.5%	Symptomatic hyperglycemia with metabolic decompensation
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If not at glycemic target (2-3 mos)

Start / Increase metformin

Start metformin immediately  
Consider initial combination with another antihyperglycemic agent

Initiate insulin +/- metformin

If not at glycemic targets

**Add an agent best suited to the individual:**

<b>Patient Characteristics</b>	<b>Agent Characteristics</b>
Degree of hyperglycemia	BG lowering efficacy and durability
Risk of hypoglycemia	Risk of inducing hypoglycemia
Overweight or obesity	Effect on weight
Comorbidities (renal, cardiac, hepatic)	Contraindications & side-effects
Preferences & access to treatment	Cost and coverage
Other	Other

See next page...

From prior page...

Add an agent best suited to the individual (agents listed in alphabetical order):

Class	Relative A1C lowering	Hypo-glycemia	Weight	Other therapeutic considerations	Cost
Alpha-glucosidase inhibitor (acarbose)	↓	Rare	neutral to ↓	Improved postprandial control, GI side-effects	\$\$
Incretin agents: DPP-4 Inhibitors	↓↓	Rare	neutral to ↓	GI side-effects	\$\$\$
GLP-1 receptor agonists	↓↓ to ↓↓↓	Rare	↓		\$\$\$\$
Insulin	↓↓↓	Yes	↑↑	No dose ceiling, flexible regimens	\$-\$\$\$\$
Insulin secretagogue: Meglitinide	↓↓	Yes	↑	Less hypoglycemia in context of missed meals but usually requires TID to QID dosing	\$\$
Sulfonylurea	↓↓	Yes	↑	Gliclazide and glimepiride associated with less hypoglycemia than glyburide	\$
TZD	↓↓	Rare	↑↑	CHF, edema, fractures, rare bladder cancer (pioglitazone), cardiovascular controversy (rosiglitazone), 6-12 weeks required for maximal effect	\$\$
Weight loss agent (orlistat)	↓	None	↓	GI side effects	\$\$\$

If not at glycemic target

- Add another agent from a different class
- Add/Intensify insulin regimen

Make timely adjustments to attain target A1C within 3-6 months

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## Stages of Chronic Kidney Disease of all Types

Stage	Qualitative Description	Renal Function (mL/min/1.73 m <sup>2</sup> )
1	Kidney damage-normal GFR	≥90
2	Kidney damage-mild ↓ GFR	60-89
3	Moderate ↓ GFR	30-59
4	Severe ↓ GFR	15-29
5	End-stage renal disease	<15 (or dialysis)

# Therapeutic considerations for renal impairment

Therapeutic considerations when using common therapies in patients with diabetes with varying degrees of renal impairment					
	CKD 1 & 2 eGFR ≥60 mL/min	CKD 3 eGFR 30-59 mL/min	CKD 4 eGFR 15-29 mL/min	CKD 5 eGFR <15 mL/min or dialysis	Comments
<b>Metformin</b>	No dose adjustment	Reduce dose	Use alternative agent		See "Sick Day Medication List" (Appendix 7). Risk of drug accumulation with declining renal function, especially if acute.
<b>Alpha-glucosidase Inhibitor</b>					
Acarbose	No dose adjustment	No dose adjustment	Use alternative agent		
<b>DPP4-Inhibitors</b>					
Linagliptin	No dose adjustment required				Experience in patients with ESRD or on dialysis is limited. Use with caution in these patients.
Saxagliptin		Lower Dose 2.5 mg once daily (<50 mL/min)		Use alternative agent	Should not be used in patients on dialysis.
Sitagliptin		Lower dose (50 mg daily) (30-49 mL/min)	Use lowest dose (25 mg daily)		Risk of accumulation.
<b>GLP-1 Receptor Agonists</b>					
Exenatide	No dose adjustment	Lower dose (5 mcg BID)	Use alternative agent		
Liraglutide	No dose adjustment	Use alternative agent (<50 mL/min)			
<b>Insulin Secretagogues</b>					
Gliclazide			Risk of hypoglycemia, consider lower dose	Risk of hypoglycemia, consider alternative agent	
Glimepiride			Risk of hypoglycemia, consider lower dose	Max 1 mg daily, consider alternative agent	Both pharmacokinetics and pharmacodynamics are altered, increasing risk of hypoglycemia.
Glyburide		Use alternative agent			Increased risk of prolonged hypoglycemia due to accumulation of parent drug and active metabolites.
Nateglinide	No dose adjustment required				
Repaglinide	No dose adjustment required				
<b>Thiazolidinediones (TZDs)</b>					
Pioglitazone	No dose adjustment required				Risk of volume overload.
Rosiglitazone	No dose adjustment required				

Antihyperglycemic Therapies



# Metformin

## Drug Dosing of Antihyperglycemics in Chronic Kidney Disease

	CKD 1 and 2	CKD 3	CKD 4	CKD 5	Comments
Metformin	None	Consider reduce dose	Consider alternative		Can accumulate in lower GFR, esp acute

# Contraindications to metformin...contraindicated?

- Lactic acidosis:
  - Occurs in type 2 DM even without metformin use
    - 9.7-16.9 events / 100,000 PY
  - With metformin use, rate is similar
    - 8-9 events / 100,000 PY
  - Lactate formation may be more coincidental and not related to metformin but due to:
    - Acute kidney injury, acute CHF, acute MI, sepsis
  - Some cases reported in setting of normal renal function, at wide doses ranges
  - Serum metformin levels do not appear to correlate with lactic acidosis

# Contraindications to metformin...contraindicated?

- Balance the risk with the benefits:
  - There may be a 1% 10 year risk with metformin use
- The benefits of metformin from UKPDS:
  - 5% reduction in diabetes-related deaths
  - 7% reduction in all-cause mortality
  - 6% reduction in myocardial infarction
  - 3% reduction in stroke

# Acarbose

## Drug Dosing of Antihyperglycemics in Chronic Kidney Disease

	CKD 1 and 2	CKD 3	CKD 4	CKD 5	Comments
Acarbose	None	None	Consider alternative		Limited information

# DPP 4 Inhibitors

Drug Dosing of Antihyperglycemics in Chronic Kidney Disease					
	CKD 1 and 2	CKD 3	CKD 4	CKD 5	Comments
Linagliptin 5 mg	None				Limited ESRD and dialysis information
Saxagliptin 5 mg	None	Reduce to 2.5 mg daily in GFR <50			Not to be used in dialysis
Sitagliptin 100 mg	None	50 mg GFR 30-49	25 mg		Risk to accumulate

Adapted 2013 CDA CPG 2013 appendix 6

# GLP-1 Receptor Agonists

## Drug Dosing of Antihyperglycemics in Chronic Kidney Disease

	CKD 1 and 2	CKD 3	CKD 4	CKD 5	Comments
Exenatide 5, 10 ug BID	None	Lower dose 5 ug BID		Use alternative	
Liraglutide 1.2, 1.8 mg OD	None	Consider alternative GFR <50**			

# Sulfonylureas

## Drug Dosing of Antihyperglycemics in Chronic Kidney Disease

	CKD 1 and 2	CKD 3	CKD 4	CKD 5	Comments
Gliclazide	None		Risk hypoglycemia Reduce dose	Risk hypo Consider alternate	ESRD and dialysis info limited
Glyburide	None	Use alternate**			Risk prolonged hypo due to accumulation

# Thiazolidinediones (TZD)

## Drug Dosing of Antihyperglycemics in Chronic Kidney Disease

	CKD 1 and 2	CKD 3	CKD 4	CKD 5	Comments
Pioglitazone	None				Theoretic volume overload risk
Rosiglitazone	None				



# SGLT2 Inhibitors

## Drug Dosing of Antihyperglycemics in Chronic Kidney Disease

	CKD 1 and 2	CKD 3	CKD 4	CKD 5	Comments
Canagliflozin 100, 300 mg	None	Do not start GFR <60 Stay at 100 mg GFR 45- 60	Use alternative GFR <45		Efficacy reduction and adverse events

# Insulin

- With declining renal function,  $\frac{1}{2}$  life of insulin increases
- Risk of hypoglycemia
- Home blood glucose monitoring frequency should be increased and dose decrease generally required
- Insulin remains the most important tool for diabetes management in low GFR

# Counsel all Patients About

# Sick Day Medication List

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## **Instructions for Healthcare Professionals:**

If patients become ill and are unable to maintain adequate fluid intake, or have an acute decline in renal function (e.g. due to gastrointestinal upset or dehydration), they should be instructed to hold medications which will:

### **A) Increase risk for a decline in kidney function:**

- Angiotensin-converting enzyme inhibitor
- Angiotensin receptor blockers
- Direct renin inhibitors
- Non-steroidal anti-inflammatory drugs
- Diuretics

### **B) Have reduced clearance and increase risk for adverse effects:**

- Metformin
- Sulfonylureas (gliclazide, glimepiride, glyburide)

**S** sulfonylureas  
**A** ACE-inhibitors  
**D** diuretics, direct renin inhibitors  
  
**M** metformin  
**A** angiotensin receptor blockers  
**N** non-steroidal anti-inflammatory

Please complete the following card and give it to your patient.

Patients should be instructed that increased frequency of self blood glucose monitoring will be required and adjustments to their doses of insulin or oral antihyperglycemic agents may be necessary.

# The bottom line

- Most hypoglycemic agents require some consideration with declining GFR
- More caution is needed in acute events or with rapidly declining GFR
- If you take away, you will need to also give